Thrombotic microangiopathy after parvovirus B19 infection treatment in a kidney transplant recipient. An uncommon presentation

Microangiopatía trombótica tras el tratamiento de infección por parvovirus B19 en trasplantado renal. Una presentación infrecuente

Dear Editor,

Parvovirus B19 (PB19) is a single-stranded DNA virus for which 90% of the population has antibodies, given that primary infection usually occurs during childhood. While PB19 infection is usually trivial in the general population,[1] in immunosuppressed patients it may manifest itself in the form of pure red cell aplasia or pancytopenia (due to the trophism of the virus towards the P antigen on the surface of erythroblasts).[2–4] It is also a cause of thrombotic microangiopathy (TMA) regardless of the degree of immunosuppression. We present here a case of pancytopenia secondary to PB19 complicated by TMA in a kidney transplant patient after withdrawal of immunosuppression.

This was a 48-year-old male with a history of chronic kidney disease resulting from chronic interstitial nephropathy in the context of repeated urinary tract infections and urinary tract malformations, having had his first and only kidney transplant and undergone a urostomy in 2014, on immunosuppression with prednisone, tacrolimus and mycophenolic acid.

Over the course of follow-up, he had progressive deterioration in renal function to baseline creatinine levels of around 4 mg/dl in association with chronic antibody-mediated rejection in July 2020 and repeated urinary tract infections related to the malformations described above.

The patient was admitted in October 2020 for asthenia and fever. Lab tests revealed a deterioration in renal function with a creatinine level of 8.36 mg/dl, metabolic acidosis, haemoglobin of 3.8 g/dl, 98,000 platelets/μl and 3200 leucocytes/μl. With these findings, he was given three units of packed red blood cells and restarted on chronic haemodialysis via a central venous catheter.

Subsequent investigation of the anaemia revealed microcytic and hyporegenerative anaemia, with no red blood cell schistocytes in the smear. However, suppressed haptoglobin and an LDH of 511 U/l were found. In view of these data, an endothelial cell culture was performed, but was negative. Coombs test, serum electrophoresis, *Leishmania* and PB19 serologies and viral loads for cytomegalovirus, BK virus and Epstein-Barr virus were negative.

With no improvement ten days after admission, a bone marrow biopsy was performed, showing hypocellular marrow with erythroid hyperplasia, *lantern* cells and viral inclusions positive for anti-PB19 antibodies (Fig. 1). Tacrolimus and mycophenolic acid were discontinued and intravenous immunoglobulins (IVIg) were started at a dose of 400 mg/kg/day for five days.

After completing the treatment, the patient's anaemia and thrombocytopenia worsened and he developed difficult-

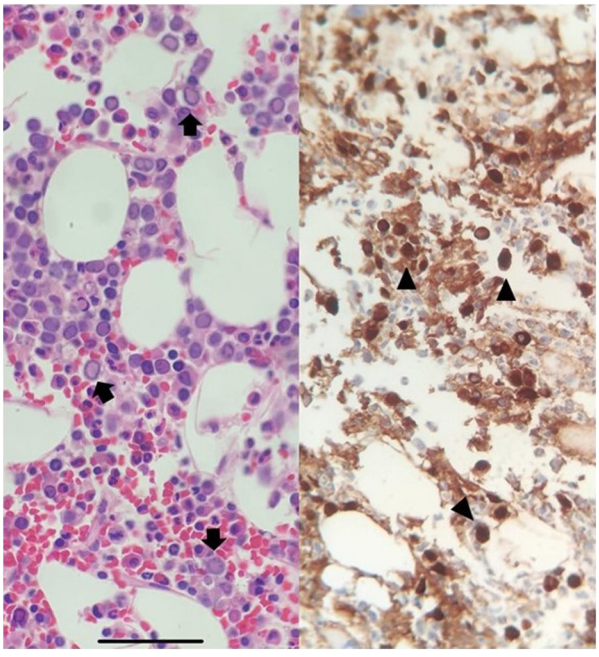

Fig. 1 – Patients bone marrow biopsy. The image on the left shows large proerythroblasts and lantern cells (arrows) (haematoxylin–eosin stain). The image on the right shows parvovirus B19 viral inclusions (arrowheads).

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Table 1 – Changes in the patient's clinical and biochemical parameters on admission, after withdrawal of immunosuppression, after three doses of eculizumab and during subsequent follow-up.

Lab test findings	On admission	After withdrawal of immunosuppression	After 3 doses of eculizumab[a]	After 1 month of follow-up[a]	After 3 months of follow-up[a]
Haemoglobin (g/dl)	3.8	7.0	8.5	10.0	11.1
Platelets ($\times 10^9$/l)	98	71	133	146	183
Peripheral blood schistocytes (per high-power field)	<1	3	<1	<1	<1
Haptoglobin (mg/dl)	<5.83	<5.83	10.30	17.60	27.50
Reticulocyte production index (%)	0.1	6.3	6.8	3.8	4.2
LDH (U/l)	511	655	286	217	256
Systolic blood pressure (mmHg)	133	199	125	146	144
Diastolic blood pressure (mmHg)	64	107	80	85	91

LDH: lactate dehydrogenase.

[a] Transfusion independence after three doses of eculizumab.

to-control hypertension (HTN), with an increase in LDH to 655 mg/dl. In addition, 6.3% reticulocytes (consistent with hyperregenerative anaemia) and three red blood cell schistocytes per field were observed in the peripheral blood smear. Donor-specific antibody testing was negative and other causes of HTN were ruled out by renal doppler.

Given the temporal relationship with the withdrawal of immunosuppression and the impossibility of performing a renal biopsy due to the high risk of bleeding, the patient was given 900 mg of eculizumab empirically every week for three weeks, achieving resolution of the haematological parameters and arterial hypertension (Table 1). However, no recovery of renal function was observed, probably because the patient already had advanced chronic kidney disease. Therefore, at discharge, the patient remained dependent on chronic haemodialysis.

Discharge serology for PB19 was positive and subsequent testing for mutations of alternative complement pathway regulatory proteins was negative.

PB19 infection usually occurs in the first year after transplantation[2] and should be suspected in patients with erythropoietin-resistant anaemia.[2,4,5] For diagnosis, the guidelines recommend determining viral load, as serology is not very sensitive in immunosuppressed patients.[2] In this case, a bone marrow biopsy was necessary given the low initial suspicion for this infection due to the amount of time since transplantation. The most common findings in bone marrow biopsy are giant proerythroblasts with intranuclear inclusions (lantern cells) (Fig. 1).

The recommended treatment[2] is IVIG at a dose of 0.4 g/kg/day for five days. In most cases, this treatment allows patients to be transfusion-independent at 12 months.[6]

After the start of treatment, the patient developed TMA. PB19-associated TMA is most commonly reported in the immediate post-transplant period.[7] Two mechanisms have been proposed as possible explanations for the development of PB19-associated TMA: direct invasion of the endothelium via the P antigen[7,8] or immune complex formation. In both cases, endothelial damage would stimulate activation of the alternative complement pathway, which would explain the good response to a short course of eculizumab.[9]

In conclusion, PB19 can trigger bone marrow aplasia in the late post-transplant period and is a rare cause of TMA which, in this case, showed significant improvement with eculizumab.

Conflicts of interest

The authors declare they have no conflicts of interest related to the publication of this article.

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What does the finding of amyloid casts in multiple myeloma mean?

¿Qué significa el hallazgo de cilindros de amiloide en el mieloma múltiple?

Dear Editor,

About 50% of patients with multiple myeloma (MM) develop various forms of renal injury during the disease[1] in, including myeloma kidney (32–48% in MM post-mortem examinations or myeloma cast nephropathy),[2] light chain amyloidosis (10–15% of cases[1] and monoclonal immunoglobulin deposition disease. Other disorders may be encountered more rarely, such as light chain proximal tubulopathy, light chain-associated acute tubulointerstitial nephritis and glomerular involvement by cryoglobulins. A far less frequently reported lesion is the finding of amyloid casts, which is challenging to comprehend, both in terms of the mechanism of their formation and their clinical significance. We are presenting a case.

He was a 57-year-old man with history of hypertension, hyperuricaemia and stage G3bA3 chronic kidney disease attributed to repeated episodes of obstructive uropathy due to calcium oxalate stones, who consulted for proteinuria. A serum monoclonal IgA lambda component of 0.84 g/dl with lambda free light chains of 1,784 mg/l and Bence Jones proteinuria of 1 g/24 h was identified. Given these findings, the patient was referred to haematology, where a bone marrow aspirate was performed, confirming the diagnosis of IgA lambda MM. It was therefore decided to perform a renal biopsy to assess renal involvement and plan a treatment.

In the renal biopsy, a maximum of three glomeruli per slice plane were counted, none of which was globally sclerosed or ischaemic and all of which retained their normal size and lobulation, and no mesangial expansion, deposits or increased cellularity were identified at any level. In the tubular lumen, casts (up to 3 mm^2) of eosinophilic material with associated histiocytic reaction were identified, which were weakly positive with periodic acid-schiff (PAS) staining, negative with the silver technique, polychromatophilic with Masson's trichrome and positive with the Congo red technique, with no positivity identified with this technique at other levels. At the tubulointerstitial level, chronic lymphocytic inflammatory infiltrate, tubular atrophy and interstitial fibrosis were also identified affecting 40% of the cortical surface. Direct immunofluorescence techniques showed strong positivity for lambda light chains in the cytoplasm of proximal tubule epithelial cells (Fig. 1).

The observed casts preented positivity for IgA, kappa and lambda light chains. Chronicity score: 4, mild chronic changes, glomerular sclerosis 0 (<10%), tubular atrophy 2 (26–50%), interstitial fibrosis 2 (26–50%), atherosclerosis 0 (intimal fibrosis < average). Ca1 (<5 casts/mm^2) T2 (atrophy/fibrosis 25–50%) according to the classification proposed by Royal et al.[3,4]

In view of the findings described above, the patient was diagnosed with myeloma cast nephropathy and chronic tubulointerstitial nephritis with mild chronic changes. A further study was performed with a fat biopsy, which did not identify an amyloid deposit, and the D-CVD regimen (daratumumab, bortezomib, cyclophosphamide and dexamethasone) was administered.

The pathogenesis of renal light chain damage involves the transformation of mesangial and tubular cells into cells of other lineages. If the transformation is to the myofibroblastic lineage, light chain disease will develop, whereas if the transformation is to the macrophage-histiocyte lineage, renal

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